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## Review

## Q1 Parkinson's disease: Autoimmunity and neuroinflammation

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## ABSTRACT

Parkinson's disease is a neurodegenerative disease that causes the death of dopaminergic neurons in the substantia nigra. The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classical parkinsonian motor symptoms. Parkinson's disease is recognized as the most common neurodegenerative disorder after Alzheimer's disease.

PD etiopathogenesis remains to be elucidated and has been connected to genetic, environmental and immunologic conditions.

The past decade has provided evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or an autoimmune response. Several autoantibodies directed at antigens associated with PD pathogenesis have been identified in PD patients. This immune activation may be the cause of, rather than a response to, the observed neuronal loss.

Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms and autonomic dysfunction. Microscopically, the specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits containing a substantial amount of α-synuclein, have been recognized.

The progression of Parkinson's disease is characterized by a worsening of motor features; however, as the disease progresses, there is an emergence of complications related to long-term symptomatic treatment.

The available therapies for Parkinson's disease only treat the symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the neurodegenerative process. Drugs that enhance the intracerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay treatment for motor symptoms.

Immunomodulatory therapeutic strategies aiming to attenuate PD neurodegeneration have become an attractive option and warrant further investigation.

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## Contents

1. Introduction	0
2. Epidemiology	0
3. Etiopathogenesis	0
4. Clinical features	0
5. Histopathology	0
6. Diagnosis	0
7. Prognosis	0
8. Treatment	0

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63	9. Conclusions. . . . .	0
64	Take-home messages. . . . .	0
65	References. . . . .	0

## 1. Introduction

Parkinson's disease is a neurodegenerative disease that results in the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resulting dopamine deficiency within the basal ganglia leads to a movement disorder characterized by classical parkinsonian motor symptoms.

Parkinson's disease was first medically described as a neurological syndrome by James Parkinson in 1817, although some aspects of Parkinson's disease were reported in earlier descriptions [1]. For example, Sylvius de la Boë wrote of resting tremor and Sauvages described festination [2,3]. Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provided descriptions that were reminiscent of Parkinson's disease [4,5]. Over 50 years later, Jean-Martin Charcot was more thorough in his descriptions and distinguished bradykinesia as a separate cardinal feature of the illness [6].

## 2. Epidemiology

Parkinson's disease is recognized as the most common neurodegenerative disorder after Alzheimer's disease [7,8]. The incidence of Parkinson's disease ranges from 10 to 18 per 100,000 person-years [9]. Gender is an established risk factor, with a male-to-female ratio of approximately 3:2 [10]. Ethnicity is also a risk factor for the disease. In the USA, the incidence is highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians and Blacks [9]. Age is the greatest risk factor for the development of Parkinson's disease. The prevalence and incidence increase nearly exponentially with age and peak after 80 years of age [11,12]. This trend has important public health implications; as the aging population and life expectancy increase worldwide, the number of people with Parkinson's disease is expected to increase by more than 50% by 2030 [7].

## 3. Etiopathogenesis

Currently, PD etiopathogenesis remains to be elucidated, and the destruction of dopaminergic neurons in PD has been connected to a

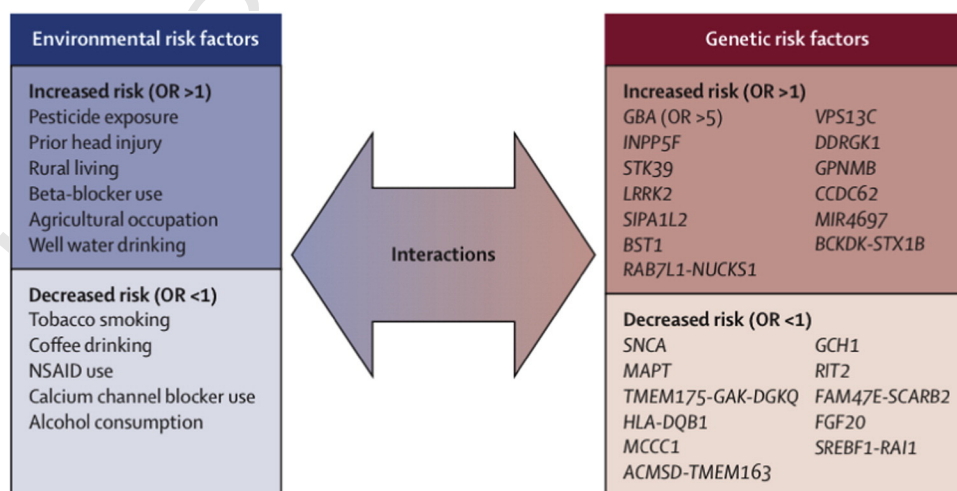
variety of factors, including genetic, environmental and immunological conditions.

Genetic factors have been identified in familial forms of PD, which contribute to approximately 10% of PD cases [13,14]. Environmental factors that were shown to be associated with a decreased risk were tobacco smoking, coffee drinking, non-steroidal anti-inflammatory drug use, calcium channel blocker use, and alcohol consumption [15]. Factors that increase the risk of developing PD were pesticide exposure, prior head injury, rural living,  $\beta$ -blocker use, agricultural occupation, and well-water drinking [15].

Furthermore, the results of epidemiological studies [15] showed that the use of anti-inflammatory medications, specifically non-steroidal anti-inflammatory drugs, reduced the risk of developing Parkinson's disease, supporting the hypothesis that inflammation might promote an underlying disease process (Fig. 1).

Currently, PD etiopathogenesis remains to be elucidated. Recently, reviews of the current literature have brought to light evidence for the possible role of the immune system, specifically autoimmune mechanisms, in the etiopathogenesis of PD [16]. Previously, it was believed that PD is not mediated by autoimmune mechanisms [17]. However, data accumulated over the past decade regarding immune alterations in PD increased the interest in pursuing such an association. A series of independent observations has led to the convergence of the view that innate and adaptive immune mechanisms might play a role in the development of PD [18].

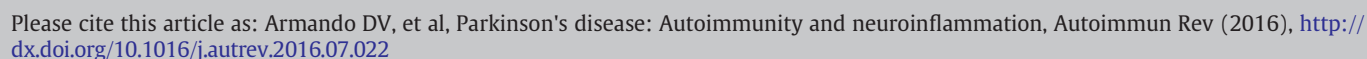
Neuroinflammation is a characteristic feature of Parkinson's disease pathology, but it has yet to be established whether neuroinflammation promotes or protects from neurodegeneration. A significant increase in the level of innate immune components, including complement and cytokines (e.g., IL-1, IL-2, IL-6, and TNF), in the substantia nigra and cerebrospinal fluid (CSF) of PD patients has been observed [18]. Elevation of  $\gamma/\delta$  + T cells in the peripheral blood and CSF of PD patients was also reported [19]. Benkler et al. [20] then further pursued this quest and found evidence suggesting that an autoimmune mechanism, which may be mediated via humoral responses, might play a role in the etiopathogenesis of PD.



**Fig. 1.** Risk factors for the development of Parkinson's disease. Results of epidemiological studies have revealed various environmental exposures that increase (OR > 1) or decrease (OR < 1) the risk of developing Parkinson's disease (left). Findings of genome-wide association studies have identified genetic risk factors, which are polymorphisms within certain genes that influence risk for developing Parkinson's disease (right). The strongest genetic risk factor is the Asn370Ser mutation of  $\beta$ -glucocerebrosidase, which is associated with an OR greater than 5. The interplay between environmental and genetic risk factors is under investigation. OR = odds ratio. (From: Lancet 2015;386:896-912).

These experiments demonstrate that the first criterion for DCs to initiate an adaptive autoimmune response directed against NM-associated structures was fulfilled. Koutsilieri et al. [28] hypothesize that activated DCs migrate from the brain into the cervical lymph node, where they present the potential (auto-)antigens to T and B cells. The recognition of NM as a pathogen or dangerous molecule and its uptake by DCs would allow the DCs to migrate, and its presentation in the cervical lymph nodes triggers an adaptive autoimmune response if NM-reactive T or B cells are present. This autoimmune response against NM would be directed against NM-rich cells in the brain, leading to dopaminergic cell death. This auto-aggressive loop would be enhanced by NM-triggered activation of microglia [29,30], resulting in an amplification of the adaptive immune response against NM and the local reactivation of the immigrating effector T cells (Fig. 2). There is accumulating evidence for an immunogenic role of NM in PD pathogenesis. Antibodies directed at catecholamine-based melanins have been detected in the sera from PD patients [21].

Taken together, these results might suggest a role for autoantibodies, which are a prominent feature of autoimmunity, in the ethiopathogenesis of PD. However, recent studies suggest that this immune activation may be the cause of, rather than a response to, the observed neuronal loss.



#### 4. Clinical features

Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor [39]. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders and autonomic dysfunction.

Non-motor features are also frequently present in Parkinson's disease before the onset of the classical motor symptoms (Fig. 1) [40]. The premotor phase can be prolonged; for example, the average latency between the onset of the early symptoms and occurrence of parkinsonian motor symptoms is 12–14 years [40].

In late-stage Parkinson's disease, treatment-resistant motor and non-motor features are prominent and include axial motor symptoms, such as postural instability, freezing of gait, falls, dysphagia, and speech dysfunction. After approximately 17 years of disease, up to 80% of patients with Parkinson's disease have a freezing of gait and falls, and up to 50% of patients report choking [41]. Dementia is particularly prevalent, occurring in 83% of patients with Parkinson's disease who have had a disease duration of 20 years [42] (Fig. 3).

#### 5. Histopathology

The loss of dark pigmentation in the substantia nigra and frontal atrophy are typical examples of macroscopic brain aberrations that develop in PD [43].

Microscopically, two predominant features have been recognized: a specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits that contain a substantial amount of  $\alpha$ -synuclein [43]. In its misfolded state,  $\alpha$ -synuclein becomes insoluble and aggregates to form intracellular inclusions within the cell body (Lewy bodies) and processes (Lewy neurites) of neurons [44]. Lewy pathology is not restricted to the brain, but can also be found in the spinal cord and peripheral nervous system [45].

#### 6. Diagnosis

A clinical diagnosis of Parkinson's disease is based on the presence of parkinsonian motor features, namely, bradykinesia, rigidity and resting tremor.

Strategies to develop biomarkers for the diagnosis of Parkinson's disease are under investigation, particularly to enable diagnosis early in the disease course, even before the onset of motor symptoms. Potential clinical markers include olfactory impairment, as measured by standard

methods, such as the University of Pennsylvania's smell identification test [40]. The proposed pathological markers are being tested on the basis of earlier findings of  $\alpha$ -synuclein within the peripheral nervous system. The concentrations of  $\alpha$ -synuclein, DJ-1, tau and  $\beta$ -amyloid [46,47], as well as the  $\beta$ -glucocerebrosidase activity in the cerebrospinal fluid are being tested as potential biochemical biomarkers of early Parkinson's disease [48,49] (Fig. 4).

Candidate imaging markers include positron emission tomography (PET) or single photon emission computed tomography (SPECT) methods to measure the reduction in the number of SNpc dopaminergic nerve terminals projecting to the striatum [50]. Standard MRI has a marginal role in Parkinson's disease diagnosis, but high and ultra-high-field (7 Tesla) MRI combined with advanced techniques, such as diffusion tensor imaging, are being explored for early diagnosis of Parkinson's disease [51,52].

For people with family members with a known monogenic form of Parkinson's disease, genetic testing can assist in the diagnosis.

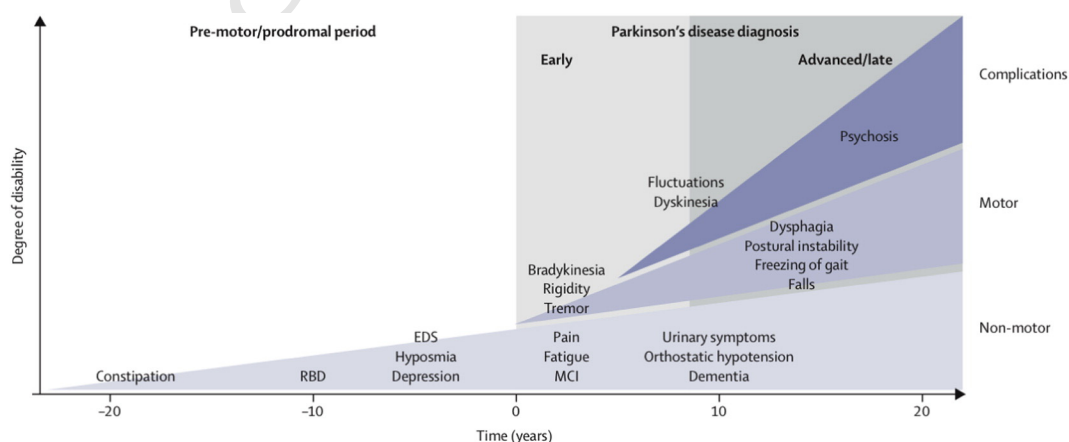
A single measure might not suffice for an accurate and early diagnosis of such a complex disease. Instead, a combination of imaging, biochemical and genetic biomarkers might be required.

#### 7. Prognosis

The progression of Parkinson's disease is characterized by the worsening of motor features, which can initially be managed with symptomatic therapies. However, as the disease progresses, there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia and psychosis [41]. Symptoms of late-stage Parkinson's disease substantially contribute to disability and are strong predictors of a need for admission to an institution and mortality [53].

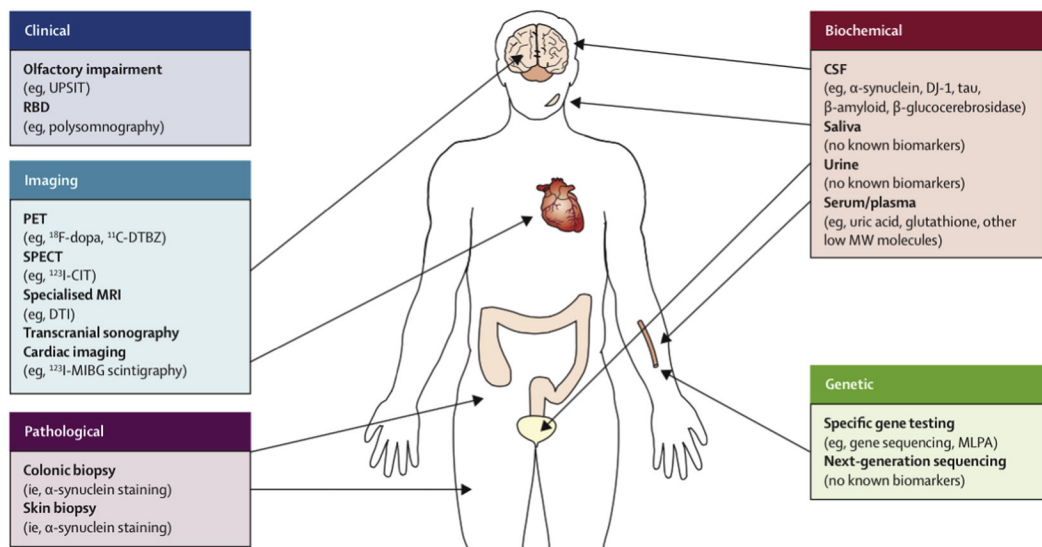
#### 8. Treatment

The available therapies for Parkinson's disease only treat the symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the underlying neurodegenerative process. Drugs that can slow or stop the neurodegenerative process in Parkinson's disease are not yet available, but such disease-modifying drugs are anticipated to be most effective if patients can be diagnosed and treated during this prodromal premotor period. Drugs that enhance intracerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay treatment for motor symptoms. These drugs include levodopa, dopamine agonists, 286



**Fig. 3.** Clinical symptoms and time course of Parkinson's disease progression. Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterized by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia and psychosis, also contribute to disability. EDS = excessive daytime sleepiness; MCI = mild cognitive impairment; RBD = REM sleep behaviour disorder. (From: Lancet 2015;386:896:912).





**Fig. 4.** Potential biomarkers for diagnosis of Parkinson's disease. A variety of biomarkers for Parkinson's disease diagnosis are currently under investigation. These biomarkers can be classified as clinical, imaging, pathological, biochemical and genetic. Midbrain hyperechogenicity detected by transcranial sonography is a proposed diagnostic biomarker for Parkinson's disease, but many experts have found this method to have reliability and replicability issues. Combinations of biomarkers are likely to be necessary for accurate diagnosis of premotor or early PD. 11C-DTBZ = 11C-dihydrotetrabenazine; CSF = cerebrospinal fluid; DTI = diffusion tensor imaging; 123I-CIT = 123I-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)tropane; 123I-MIBG = 123I-metaiodobenzylguanidine; MLPA = multiplex ligation-dependent probe amplification; MW = molecular weight; PET = positron emission tomography; RBD = rapid eye movement sleep behaviour disorder; SPECT = single photon emission computed tomography; UPSIT = University of Pennsylvania's smell identification test. (From: Lancet 2015;386:896:912).

monoamine oxidase type B inhibitors and, less commonly, amantadine [54,55]. Because none of these drugs have proven to be neuroprotective or disease-modifying, therapy does not need to be started at the time of diagnosis for all patients. However, there is little justification for delay. Treatment should be initiated when symptoms cause disability or discomfort to the patient, with the goal of improving function and quality of life.

The past decade has provided accumulating evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or an autoimmune response. Thus, immunomodulatory therapy strategies aiming to attenuate PD disease progression have become an attractive option and warrant further investigation. However, the negative results of non-steroidal anti-inflammatory drugs in late PD [56] strongly suggest that early immunomodulation is the key to preventing PD onset and progression.

Minocycline, a broad-spectrum tetracycline antibiotic, has been tested in experimental models and PD patients. Minocycline effectively crosses the blood–brain barrier (BBB) and shows potent anti-inflammatory effects in neurotoxin models of PD [57]. A randomized, double-blind, Phase II clinical trial showed that minocycline offers a clinical benefit to early PD patients, which warrants further consideration of minocycline for use in Phase III clinical trials [58].

Leucine-rich repeat kinase 2 (LRRK2) is an enzyme that is highly expressed in peripheral macrophages and monocytic cells, as well as central microglia, suggesting a functional role for LRRK2 in the innate immune system [59,60]. Inhibition or attenuation of LRRK2 is a promising therapeutic strategy as an anti-inflammatory treatment for PD.

Peroxisome proliferator-activated receptor gamma coactivator 1- $\alpha$  (PGC-1 $\alpha$ ) is a potential new target for anti-inflammatory therapy in PD patients. PGC-1 $\alpha$  activity is mainly controlled by the peroxisome proliferator-activated receptors (PPARs), 5' AMP-activated protein kinase (AMPK), and sirtuin 1 (Sirt1) [61]. Hence, pharmacological activators for these proteins have the potential to exert anti-inflammatory effects by activating PGC-1 $\alpha$ . These activators include fibrates and rosiglitazone (PPAR) [62,63], metformin [64], pyrroloquinoline quinone [65], 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) (AMPK) [66] and resveratrol (Sirt1) [67].

As PPAR agonists (fibrates and rosiglitazone) and AMPK activators (metformin and AICAR) are already routinely used in clinical practice for the treatment of metabolic syndrome and type 2 diabetes, these drugs could be readily translated from animal models to PD patients. Preclinical CNS distribution and efficacy studies using inflammatory animal models of PD will be sufficient to warrant clinical trials on these drugs.

## 9. Conclusions

Parkinson's disease is a debilitating disease of unknown cause, despite major scientific and therapeutic advances. The extensive damage to the dopaminergic system in PD seems to be interconnected with genetics, environmental and immunological factors, which is described as a mosaic of many autoimmune diseases [68]. In this review, we pursued the evidence for immune- and autoimmune-mediated mechanisms that are associated with PD. A unique observation indicated that olfactory dysfunction may be a consequence of an autoimmune mechanism. As decreased olfaction is one of the earliest non-motor signs of PD, this observation might shed more light on a possible association between autoimmunity and PD.

The prevalence of several brain-associated autoantibodies in the sera of PD patients further support the possible role of immunoglobulin-mediated autoimmune mechanisms in the etiopathogenesis of PD. Not only can these autoantibodies serve as biomarkers of disease but our renewed understanding of the nature of this complex disease might also be useful for the early diagnosis and treatment of PD patients. It is even safe to say that novel therapeutics targeted at specific autoantibodies may be able to differentiate between PD subgroups. Further studies to evaluate a larger number of patients and preferably a wider profile of brain-associated autoantibodies might enable a better understanding of the precise etiopathological mechanism of PD.

Thus, although PD pathogenesis remains to be fully elucidated, it seems that the inflammation and neuronal degeneration associated with PD could be induced by autoimmune mechanisms, mainly via brain-specific auto-Abs.

## Take-home messages

- Parkinson's disease is a neurodegenerative disease that causes the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classic parkinsonian motor symptoms.
- PD etiopathogenesis remains to be elucidated and has been connected to genetic, environmental and immunological conditions. Recently, the role of autoimmune mechanisms in the etiopathogenesis of PD has garnered more attention. Thus, it seems that neuronal degeneration could be induced by autoimmune mechanisms, mainly via brain-specific autoantibodies.
- Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms and autonomic dysfunction. Olfactory impairment is one of the first symptoms and allows an early diagnosis of PD many years before the onset of motor symptoms.
- Microscopically, two predominant features have been recognized: a specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits containing a substantial amount of  $\alpha$ -synuclein.
- Therapies for Parkinson's disease only treat the symptoms of the disease. Drugs that enhance the intracerebral dopamine concentrations (levodopa) or stimulate dopamine receptors (dopamine agonists) remain the mainstay treatment for motor symptoms. A major goal of Parkinson's disease research is the development of disease-modifying drugs that stop the neurodegenerative process.

If NM-reactive lymphocytes are present, they get activated (primed) and secrete NM-specific antibodies (B cells) or exert NM-specific cytotoxic functions (T cells). Activation of microglia by NM would result in a proliferation of NM-specific T cells after contact with NM-presenting microglia. NM-specific antibodies and T cells may recognize NM-positive neurons and trigger their degradation. (From: J Neural Transm 2013;120:75–81).

## References

- [1] Parkinson J. An essay on the shaking palsy. Whittingham and Rowland for Sherwood. London: Needly and Jones; 1817.
- [2] Sylvius de la Boë F. Opera Medica. Danielel Elsevirum et Abrahamum Wolfgang. Amsterdam; 1680.
- [3] Tyler K. A history of Parkinson's disease. In: WC K, editor. Handbook of Parkinson's disease. New York: Marcel Dekker; 1992. p. 1–34.
- [4] Manyam BV, Sánchez-Ramos JR. Traditional and complementary therapies in Parkinson's disease. Adv Neurol 1999;80:565–574.
- [5] Zhang Z-X, Dong Z-H, GC R'n. Early descriptions of Parkinson's disease in ancient China. Arch Neurol 2006;63:782–784.
- [6] Charcot J-M. On Parkinson's disease. Lectures on diseases of the nervous system delivered at the Salpêtrière. London: New Sydenham Society; 1877. p. 129–156.
- [7] Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007;68:384–386.
- [8] Alzheimer's Association. 2014 Alzheimer's disease facts and figures. Alzheimers Dement 2014;10:e47–92.
- [9] Van Den Eeden SK. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 2003;157:1015–1022.
- [10] De Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5:525–535.
- [11] Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 2009;72:432–438.
- [12] Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2014;29:1583–1590.
- [13] Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet 2009;18:R48–59.
- [14] Rosner S, Giladi N, Orr-Urtreger A. Advances in the genetics of Parkinson's disease. Acta Pharmacol Sin 2008;29:21–34.
- [15] Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012;72:893–901.

- [16] Benkler M, Agmon-Levin N, Shoenfeld Y. Parkinson's disease, autoimmunity, and olfaction. Int J Neurosci 2009;119:2133–2143.
- [17] Møller A, Perrild H, Pedersen H, Høier-Madsen M. Parkinson's disease and autoimmunity. Acta Neurol Scand 1989;79:173–175.
- [18] Liu B, Gao HM, Hong JS. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injury: role of neuroinflammation. Environ Health Perspect 2003;111:1065–1073.
- [19] Fiszer U, Mix E, Fredrikson S, Kostulas V, Olsson T, Link H. Gamma delta + T cells are increased in patients with Parkinson's disease. J Neurol Sci 1994;121:39–45.
- [20] Benkler M, Agmon-Levin N, Hassin-Baer S, Cohen OS, Ortega-Hernandez OD, Levy A, et al. Immunology, autoimmunity, and autoantibodies in Parkinson's disease. Clin Rev Allergy Immunol 2012;42:164–171.
- [21] Double KL, Rowe DB, Carew-Jones FM, Hayes M, Chan DK, Blackie J, et al. Anti-melanin antibodies are increased in sera in Parkinson's disease. Exp Neurol 2009;217:297–301.
- [22] Papachroni KK, Ninkina N, Papapanagiotou A, Hadjigeorgiou GM, Xiromerisiou G, Papadimitriou A, et al. Autoantibodies to alpha-synuclein in inherited Parkinson's disease. J Neurochem 2007;101:749–756.
- [23] Yanamandra K, Gruden MA, Casate V, Meskys R, Forsgren L, Morozova-Roche LA. Alpha-synuclein reactive antibodies as diagnostic biomarkers in blood sera of Parkinson's disease patients. PLoS One 2011;6:e18513.
- [24] Zappia M, Cresciene L, Bosco D, Arabia G, Nicoletti G, Bagala A, et al. Anti-GM1 ganglioside antibodies in Parkinson's disease. Acta Neurol Scand 2002;106:54–57.
- [25] Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. Brain 2005;128:2665–2674.
- [26] Graham DG. On the origin and significance of neuromelanin. Arch Pathol Lab Med 1979;103:359–362.
- [27] Oberlander U, Pletinckx K, Dohler A, Muller N, Lutz MB, Arzberger T, et al. Neuromelanin is an immune stimulator for dendritic cells in vitro. BMC Neurosci 2011;12:116.
- [28] Koutsilieri E, Lutz MB, Scheller C. Autoimmunity, dendritic cells and relevance for Parkinson's disease. J Neural Transm 2013;120:75–81.
- [29] Wilms H, Rosenstiel P, Sievers J, Deuschl G, Zecca L, Lucius R. Activation of microglia by human neuromelanin is NF-kappaB dependent and involves p38 mitogen-activated protein kinase: implications for Parkinson's disease. FASEB J 2003;17:500–2.
- [30] Zhang W, Phillips K, Wielgus AR, Liu J, Albertini A, Zucca FA, et al. Neuromelanin activates microglia and induces degeneration of dopaminergic neurons: implications for progression of Parkinson's disease. Neurotox Res 2011;19:63–72.
- [31] Carvey PM, McRae A, Lin TF, Ptak LR, Lo ES, Goetz CG, et al. The potential use of dopamine neuron antibody and a striatal-derived neurotrophic factor as diagnostic markers in Parkinson's disease. Neurology 1991;41:53–8.
- [32] Le WD, Rowe DB, Jankovic J, Xei W, Apple SH. Effects of cerebrospinal fluid from patients with Parkinson disease on dopaminergic cells. Arch Neurol 1999;56:194–200.
- [33] Chen S, Le WD, Xie WJ, Alexianu ME, Engelhardt JJ, Siklos L, et al. Experimental destruction of substantia nigra initiated by Parkinson disease immunoglobulins. Arch Neurol 1998;55:1075–80.
- [34] He Y, Le WD, Appel SH. Role of FCγ receptors in nigral cell injury induced by Parkinson's disease immunoglobulin injection into mouse substantia nigra. Exp Neurol 2002;176:322–7.
- [35] Abramsky O, Litvin Y. Autoimmune response to dopamine-receptor as a possible mechanism in the pathogenesis of Parkinson's disease and schizophrenia. Perspect Biol Med 1978;22:104114.
- [36] Luedtke RR, Griffin SA, Conroy SS, Jin X, Pinto A, Sesack SR. Immunoblot and immunohistochemical comparison of murine monoclonal antibodies specific for the rat D1a and D1b dopamine receptor subtypes. J Neuroimmunol 1999;101:170–87.
- [37] Myers PR, Donlon M, McCarthy K, Livengood D, Shain W. Evidence for a dopamine receptor antibody. Biochem Biophys Res Commun 1976;72:1311–8.
- [38] Farooqui SM, Brock JW, Hamdi A, Prasad C. Antibodies against synthetic peptides predicted from the nucleotide sequence of D2 receptor recognize native dopamine receptor protein in rat striatum. J Neurochem 1991;57:1363–1369.
- [39] Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.
- [40] Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord 2012;27:617–626.
- [41] Hely MA, Morris JGL, Reid WGJ, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20:190–199.
- [42] Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837–844.
- [43] Lerler A, Bagic A. Olfactory pathogenesis of idiopathic Parkinson disease revisited. Mov Disord 2008;23:1076–84.
- [44] Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nat Rev Neurol 2012;9:13–24.
- [45] Iwanaga K, Wakabayashi K, Yoshimoto M, Tomita I, Satoh H, Takashima H, et al. Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. Neurology 1999;52:1269–1271.
- [46] Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med 2011;1:a008862.
- [47] Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, et al. Cofee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. Eur J Neurol 2011;18:756–765.
- [48] Hong Z, Shi M, Chung KA, Quinn JF, Peskind ER, Galasko D, et al. DJ-1 and  $\alpha$ -synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. Brain 2010;133:713–726.

- [49] Parnetti L, Castrioto A, Chiasserini D, Persichetti E, Tambasco N, El-Agnaf O, et al. Cerebrospinal fluid biomarkers in Parkinson disease. *Nat Rev Neurol* 2013;9:131–140. 518
- [50] Brooks DJ, Pavese N. Imaging biomarkers in Parkinson's disease. *Prog Neurobiol* 2011;95:614–628. 519
- [51] Lehericy S, Sharman MA, Santos CLD, Paquin R, Gallea C. Magnetic resonance imaging of the substantia nigra in Parkinson's disease. *Mov Disord* 2012;27:822–830. 520
- [52] Lehericy S, Bardin E, Poupon C, Vidailhet M, Francois C. 7 tesla magnetic resonance imaging: a closer look at substantia nigra anatomy in Parkinson's disease. *Mov Disord* 2014;29:1574–1581. 521
- [53] Coelho M, Ferreira JJ. Late-stage Parkinson disease. *Nat Rev Neurol* 2012;8:435–442. 522
- [54] Fox SH, Katzenschlager R, Lim SY, Ravina B, Seppi K, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2011;26:S2–41. 523
- [55] Connolly B, Lang AE. Pharmacological treatment of Parkinson's disease: a review. *JAMA* 2014;311:1670–1683. 524
- [56] Ton TG, Heckbert SR, Longstreth Jr WT, Rossing MA, Kukull WA, Franklin GM, et al. Non steroidal anti-inflammatory drugs and risk of Parkinson's disease. *Mov Disord* 2006;21:964–969. 525
- [57] Plane JM, Shen Y, Pleasure DE, Deng W. Prospects for minocycline neuroprotection. *Arch Neurol* 2010;67:1442–1448. 526
- [58] Ravina B. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology* 2006;66:664–671. 527
- [59] Thevenet J, Pescini Gobert R, van Huijsduijnen R H, Wiessner C, YJ S. Regulation of LRRK2 expression points to a functional role in human monocyte maturation. *PLoS One* 2011;6:e21519. 528
- [60] Moehle MS, Webber PJ, Tse T, Sukar N, Standaert DG, DeSilva TM, et al. LRRK2 inhibition attenuates microglial inflammatory responses. *J Neurosci* 2012;32:1602–1611. 529
- [61] Wenz T. PGC-1 $\alpha$  activation as a therapeutic approach in mitochondrial disease. *IUBMB Life* 2009;61:1051–1062. 530
- [62] Hondares E, Pineda-Torra I, Iglesias R, Staels B, Villarroja F, Giral M. PPAR $\delta$ , but not PPAR $\alpha$ , activates PGC-1 $\alpha$  gene transcription in muscle. *Biochem Biophys Res Commun* 2007;354:1021–1027. 531
- [63] Pardo R, Enguix N, Lasheras J, Feliu JE, Kralli A, Villena JA. Rosiglitazone-induced mitochondrial biogenesis in white adipose tissue is independent of peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$ . *PLoS One* 2011;6:e26989. 532
- [64] Suwa M, Egashira T, Nakano H, Sasaki H, Kumagai S. Metformin increases the PGC-1 $\alpha$  protein and oxidative enzyme activities possibly via AMPK phosphorylation in skeletal muscle in vivo. *J Appl Physiol* 2006;101:1685–92. 533
- [65] Chohanadisai W, Bauerly KA, Tchapanian E, Wong A, Cortopassi GA, Rucker RB. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1 $\alpha$  expression. *J Biol Chem* 2010;285:142–52. 534
- [66] Irrcher I, Ljubicic V, Kirwan AF, Hood DA. AMP activated protein kinase-regulated activation of the PGC-1 $\alpha$  promoter in skeletal muscle cells. *PLoS One* 2008;3:e3614. 535
- [67] Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 $\alpha$ . *Cell* 2006;127:1109–1122. 536
- [68] Shoenfeld Y, Blank M, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, et al. The mosaic of autoimmunity: prediction, autoantibodies and therapy in autoimmune disease. *IMAJ* 2008;10:13–9. 537